Claim 2 has been amended to further clarify the claim as requested by the Examiner request. Amendment of Claim 2 finds support in Claim 2 and throughout the specification as originally filed.

Claim 5 has been added to specifically recite recombinant expression vectors comprising the isolated nucleic acid molecule of Claim 1. Support for this claim can be found throughout the specification and in claim 1 as originally filed, with particular support being found in at least at page 17, line 10-15.

Claim 6 has been added to specifically recite host cells comprising the recombinant expression vectors of claim 5. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page17, lines 15-18.

Claim 7 has been added to specifically recite recombinant expression vectors comprising the isolated nucleic acid molecule of Claim 1. Support for this claim can be found throughout the specification and in claim 1 as originally filed, with particular support being found in at least at page 17, line 10-15.

Claim 8 has been added to specifically recite host cells comprising the recombinant expression vectors of claim 7. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page17, lines 15-18.

As these amendments to claims 1 and 2 and new claims 5-8 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry, therefore, is respectfully requested.

III. Objections

The Action objects to the oath or declaration as being defective due to non-initialed and non-dated alterations having been made. A new Declaration is enclosed to replace the earlier version and successfully address this objection.

The Action objects to the specification due to reference of patent applications in the disclosure (page 4, lines 17-19). The status of these applications have been updated by replacement of patent application numbers with appropriate U.S. Patent Numbers in the replacement paragraph described in the Amendments section above. Please note that U.S. Application No 08/820,521 gave rise to both U.S. Patent Nos. 5,942,416 and 6,277,960.

The Action objects to the title of the invention in that it is alleged to be non-descriptive. Therefore the title has been amended to read "Novel Human G Protein Coupled Receptor and Polynucleotides Encoding the Same".

IV. Rejection of Claims Under 35 U.S.C. § 101

The Action rejects claims 1-4 under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse. The Action at page 3, lines 5-7 incorrectly states that "Specifically, claims 1-4 are directed to an isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleic acid sequence..." Applicants respectfully submit that claims 3 and 4 recite full-length molecules, not isolated nucleic acid molecule comprising at least 24 contiguous bases.

The present invention has a number of substantial and credible utilities. As taught in the application and as well known to those of skill in the art, G protein coupled receptors (GPCRs) play a critical role in, *intra alia*, signal transduction and cell activation. In fact, many oncogenes are linked to GPCRs and GPCRs are the target of many pharmaceuticals. Therefore, the identification of a new and novel human GPCR has great utility.

The first issue raised in the Action is that it is unclear that the present invention is a GPCR. For example, included in the Action's reasons for the alleged lack of utility is that "However, the instant specification does not teach any physiologic ligands or functional characteristics of the NGPCR polypeptide and polynucleotide." (Action at page 3 lines 16-18). Applicants respectfully submit that any such ligand would likely be considered a distinct invention. The Action suggests that the disclosure does not provide any experimental data or information on whether the claimed proteins actually function like GPCRs (Action at page 3). However, this emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility. Given that over half of the current drugs on the market address GPCR proteins, there can be no question that those skilled in the art recognize the pharmaceutical utility of GPCR proteins.

Additionally, methods similar to those of the present invention were used to identify the GPCR of issued U.S. Patent 6,043,052. Issued U.S. Patents are presumed to be valid and to meet the

requirements of 35 U.S.C. §§ 101, 102, 103 and 112, specifically, that they have utility, are novel, non-obvious, are enabled, meet the written description requirements and particularly point out and distinctly claim the invention. Therefore, the Applicants' assertion that the described GPCR is in fact a GPCR is supported by issued U.S. Patent 6,043,052, as well as the plethora of other GPCR patents that the office has issued. For example, the specific and substantial utility of human GPCRs is evidenced by the fact that they are the subject of the above mentioned U.S. Patent No. 6,043,052 which discloses polynucleotides encoding a novel GPCR and U.S. Patent Nos. 5,891,646 and 6,110,693, both of which disclose and claim methods for detecting GPCR activity *in vivo* and *in vitro*, methods for assaying GPCR activity, and methods of screening for GPCR ligands, GPCR kinase activity, components that interact with GPCR regulatory processes and constructs useful in such methods. The issuance of these U.S. patents clearly indicates that GPCR polynucleotides have utility and that such utilities were sufficiently specific and substantial to warrant the issuance of U.S. patents directed to methods used to identify and characterize GPCRs. The teachings of these patentable disclosures are directly applicable to the present invention (GPCR polynucleotides) and are evidence that those skilled in the art recognize the specific and substantial utility of GPCRs. In light of the issuance of U.S. Patent No. 6,043,052 on polynucleotides encoding a novel GPCR, Applicants respectfully submit that the present application, which also describes polynucleotides encoding a novel GPCR, describes an invention with specific and substantial utility fully compliant with 35 U.S.C. § 101.

The question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. <u>This is not a new issue; it is one which we would have thought had been settled by case law years ago</u>.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

While such information is clearly not a prerequisite to patentability, it can be disclosed that the novel GPCR of the present invention contains a high degree of nucleic acid homology with known odorant receptors (for example, GenBank accession No. U86270, among many others) and that the amino acid sequence of the novel GPCR of the present invention is identical to SwissProt Accession No. P58173 (gi 14423785), human olfactory receptor 2B6 (Hs6M1-32) (Olfactory receptor 6-31), as shown in Exhibit D. Clearly, as this protein was annotated by those of skill in the art in no way associated with Applicants, Applicants' assertion regarding the function and utility of the protein of the present invention is credible.

Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35 U.S.C. § 101, and the Examiner's rejection should be withdrawn.

Although the above discussion is believed to be dispositive of the utility issue, the Applicants would like to further direct the Examiner's attention to the parts of the specification (Sections 5.0 and 5.1) that describe the use of sequences in a gene chip format to provide a high throughput analysis of the relevant cellular "transcriptome".

Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are

many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe a novel gene encoding a transporter and provide a unique identifier of the corresponding gene. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences encode a novel human channel protein as detailed throughout the specification. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips.

The Examiner is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in the time and resources that are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such gene chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Moreover, the presently described novel transporter provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

Yet another example of the utility of the present invention is in expanding the utility of data coming from the human genome project. Persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data

in general, and specifically human genomic data. All current therapeutics directly or indirectly interact with biological sequences encoded by the human genome, and virtually all future human therapeutics shall do likewise. Consequently, billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (C.C.P.A. 1964); *In re Malachowski*, 189 USPQ 432 (C.C.P.A. 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons that in-turn encode polypeptide sequences. The presently described cDNAs provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the described cDNA sequences define which exons are actually spliced together to produce an active transcript (*i.e.*, such sequences are generally required to conclusively identify functional exon splice-junctions). The Applicants submit that one skilled in the art would have clearly understood that the above *substantial and specific* utilities as inherent features of the presently described sequences.

For the many convincing reasons described above, the present invention clearly has specific, substantial, credible and well established utility. Therefore, Applicants submit that the rejection of claims 1-4 under 35 U.S.C. § 101 has been overcome and the Examiner is respectfully requested to withdraw the pending rejection of claims 1-4 under 35 U.S.C. § 101.

V. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported

by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-4 have been shown to have a specific, substantial, credible and well established utility, as detailed in section IV above. Applicants therefore respectfully request that the rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Action also rejects claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to enable their use. As discussed in section IV above, given the preponderance of art on the subject of GPCRs, the plethora of issued U.S. Patents describing GPCRs, the fact that many of the drugs on the market target GPCRs and the information provided by the disclosure of the present invention there can be no doubt that those skilled in the art would clearly know how to make and use the claimed invention without undue experimentation. Portions of the nucleic acid and amino acid sequences of the GPCR of the present invention provide a method of manipulating and utilizing the sequences as probes in diagnostic and prognostic assays for example. They also provide a reasonable scope of coverage for the invention described in the present disclosure.

The Action also rejects claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

Applicants submit that the written description requirement was met by the application as originally filed. 35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do

with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. A polynucleotide comprising 80 contiguous bases of the nucleotide sequence described in SEQ ID NO: 1, could be clearly identified using SEQ ID NO:1 and the ability to count. Likewise, one of skill in the art would also be able to recognize whether that any fifty contiguous amino acids were or were not present in the amino acid sequence of SEQ ID NO: 2. Polynucleotides comprising the nucleotide sequence of SEQ ID NO: 1, or a nucleotide sequence that encodes SEQ ID NO: 2, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1 and 2 thus meet the written description requirement. If one knows the full-length sequences (which are described in SEQ ID NOS: 1 and 2 of the Sequence Listing), one also knows a fragment comprising 24 or 80 contiguous nucleotides derived from said sequences. The Action cites *Fiers v. Revel*, 25 USPQ2d 1601at 1606 (CAFC 1993) and *Amgen, Inc.. v. Chugai Pharmaceutical Co.. Ltd.,* 18 USPQ2d 1016 as evidence that "the nucleic acid itself is required" (Action at page9, line 6-7). Applicants respectfully submit that the nucleic acid itself has been provided.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, has been overcome. Therefore, Applicants respectfully request that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph for failing to meet written description requirements be withdrawn.

VI. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claims 1 and 2, as allegedly indefinite based on missing words which render the claims unclear. The first example was in claim 1, which has been amended to comply with suggested language. The second example was in claim 2, which has been amended to comply with suggested language. The final example was the use of the term "NGPCR" in Claim 1. Claim 1 has been amended to omit the offending term. Thus all of these rejections have been avoided by amendment of claims 1 and 2. Therefore, the Examiner is respectfully requested to withdraw these pending rejections of claims 1 and 2 under 35 U.S.C. § 112, second paragraph.

The Action also rejects Claim 2 for allegedly providing an ambiguous definition for the phrase "hybridizes under stringent conditions". Although Applicants believe that this claim as originally filed sufficiently points out and distinctly claims the invention, in order to more rapidly progress the case to allowance, Applicants have amended Claim 2, as requested, to include specific wash conditions. Applicants respectfully submit that this rejection has thus been avoided by Applicant's amendment of Claim 2 to specify wash conditions. Accordingly, the Examiner is respectfully requested to withdraw the pending rejection of Claim 2 under 35 U.S.C. § 112, second paragraph.

VII. Rejection of Claim 1 Under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Adams *et al.*, (Accession Number AQ077154, August, 1998). While Applicants do not necessarily agree with the present rejection, Claim 1 has been amended to recite an isolated nucleic acid molecule comprising at least 80 contiguous bases of the nucleotide sequence described in SEQ ID NO: 1. Applicants submit that the rejection of Claim 1 under 35 U.S.C. § 102(b) has been thus avoided and respectfully request withdrawal of the pending rejection of claim 1 under 35 U.S.C. § 102(b).

VIII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Bunner have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

This response is timely filed and Applicants believe no fees are due in connection with this response. However, should this be incorrect the Commissioner is authorized to charge any required fees or credit any overpayment to Deposit Account No. 50-0892.

Respectfully submitted,

July 12, 2002

Date

Lance K. Ishimoto Reg. No. 41,866

LEXICON GENETICS INCORPORATED

Telephone No.: (281) 863-3333

Enclosures

24231

PATENT TRADEMARK OFFICE

Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/755,017

1. (Amended) An isolated nucleic acid molecule comprising at least 80 contiguous bases of the nucleotide sequence described in SEQ ID NO: 1.

2. (Amended) An isolated nucleic acid molecule comprising a sequence that:

(a) encodes at least fifty contiguous amino acids of the amino acid sequence of SEQ ID NO: 2; and

(b) hybridizes under stringent conditions with wash conditions of 0.1xSSC/0.1% SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising the nucleic acid sequence presented in SEQ ID NO: 1.

4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2.

5. (NEW) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 1.

6. (NEW) A host cell comprising the recombinant expression vector of claim 5.

7. (NEW) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 4.

8. (NEW) A host cell comprising the recombinant expression vector of claim 7.

Exhibit B

Marked-up Version of The Pending Claims in U.S. Patent Application Ser. No. 09/755,017

1.(Amended) An isolated nucleic acid molecule comprising at least [24] 80 contiguous bases of the nucleotide sequence [first disclosed in the NGPCR polynucleotide sequence] described in SEQ ID NO: 1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes at least fifty contiguous [the] amino acids of the amino acid sequence of [shown in] SEQ ID NO: 2; and

(b) hybridizes under stringent conditions with wash conditions of 0.1xSSC/0.1%SDS at 68°C to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising the nucleic acid sequence presented in SEQ ID NO: 1.

4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2.

5. (NEW) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 1.

6. (NEW) A host cell comprising the recombinant expression vector of claim 5.

7. (NEW) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 4.

8. (NEW) A host cell comprising the recombinant expression vector of claim 7.

Exhibit C

Marked-up Version of The Amended Paragraph and Title

in U.S. Patent Application Ser. No.09/755,017

Replaced paragraph from page 4, lines 15-22

Because of their biological significance, 7TM, and particularly GPCR, proteins have been subjected to intense scientific/commercial scrutiny (see, for example, [U.S. Applic. Ser. Nos. 08/820,521, filed March 19, 1997, and 08/833,226, filed April 17, 1997, both of] U.S. Patent Nos. 5,942,416, 6,277,960 and 5,891,720, which are herein incorporated by reference in their entirety, which describe a variety of applications and uses for GPCR sequences such as the presently described NGPCR).

Replaced Titile from page 1

NOVEL HUMAN [MEMBRANE PROTEIN] G PROTEIN COUPLED RECEPTOR AND POLYNUCLEOTIDES ENCODING THE SAME

```
 FASTA searches a protein or DNA sequence data bank
 version 3.3t05 March 30, 2000
Please cite:
 W.R. Pearson & D.J. Lipman PNAS (1988) 85:2444-2448

/tmp/fastaCAAw9a4gg: 313 aa
 >hGPR_29
 vs  /tmp/fastaDAAx9a4gg library
searching /tmp/fastaDAAx9a4gg library

    313 residues in     1 sequences

FASTA (3.34 January 2000) function [optimized, BL50 matrix (15:-5)] ktup: 2
 join: 37, opt: 25, gap-pen: -12/ -2, width:  16
 Scan time:  0.017
The best scores are:                                      opt
sp|P58173|O2B6_HUMAN Olfactory receptor 2B6 (Hs6M  ( 313) 2041

>>sp|P58173|O2B6_HUMAN Olfactory receptor 2B6 (Hs6M1-32)  (313 aa)
 initn: 2041 init1: 2041 opt: 2041
Smith-Waterman score: 2041;  100.000% identity in 313 aa overlap (1-313:1-313)

               10        20        30        40        50        60
hGPR_2 MNWVNDSIIQEFILLGFSDRPWLEFPLLVVFLISYTVTIFGNLTIILVSRLDTKLHTPMY
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
sp|P58 MNWVNDSIIQEFILLGFSDRPWLEFPLLVVFLISYTVTIFGNLTIILVSRLDTKLHTPMY
               10        20        30        40        50        60

               70        80        90       100       110       120
hGPR_2 FFLTNLSLLDLCYTTCTVPQMLVNLCSIRKVISYRGCVAQLFIFLALGATEYLLLAVMSF
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
sp|P58 FFLTNLSLLDLCYTTCTVPQMLVNLCSIRKVISYRGCVAQLFIFLALGATEYLLLAVMSF
               70        80        90       100       110       120

              130       140       150       160       170       180
hGPR_2 DRFVAICRPLHYSVIMHQRLCLQLAAASWVTGFSNSVWLSTLTLQLPLCDPYVIDHFLCE
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
sp|P58 DRFVAICRPLHYSVIMHQRLCLQLAAASWVTGFSNSVWLSTLTLQLPLCDPYVIDHFLCE
              130       140       150       160       170       180

              190       200       210       220       230       240
hGPR_2 VPALLKLSCVETTANEAELFLVSELFHLIPLTLILISYAFIVRAVLRIQSAEGRQKAFGT
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
sp|P58 VPALLKLSCVETTANEAELFLVSELFHLIPLTLILISYAFIVRAVLRIQSAEGRQKAFGT
```

```
              190       200       210       220       230       240

              250       260       270       280       290       300
hGPR_2 CGSHLIVVSLFYSTAVSVYLQPPSPSSKDQGKMVSLFYGIIAPMLNPLIYTLRNKEVKEG
       ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
sp|P58 CGSHLIVVSLFYSTAVSVYLQPPSPSSKDQGKMVSLFYGIIAPMLNPLIYTLRNKEVKEG
              250       260       270       280       290       300

              310
hGPR_2 FKRLVARVFLIKK
       :::::::::::::
sp|P58 FKRLVARVFLIKK
              310



313 residues in 1 query   sequences
313 residues in 1 library sequences
 Scomplib [version 3.3t05 March 30, 2000]
 start: Tue Jul  9 13:39:57 2002 done: Tue Jul  9 13:39:57 2002
 Scan time:  0.017 Display time:  0.133

Function used was FASTA
```

☐ 1: P58173. Olfactory recepto... [gi:14423785]

BLink, Domains, Related Sequences, Domain Relatives, Taxonomy, LinkOut

```
LOCUS       O2B6_HUMAN               313 aa            linear   PRI 15-JUN-2002
DEFINITION  Olfactory receptor 2B6 (Hs6M1-32) (Olfactory receptor 6-31)
            (OR6-31).
ACCESSION   P58173
VERSION     P58173  GI:14423785
DBSOURCE    swissprot: locus O2B6_HUMAN, accession P58173;
            class: standard.
            extra accessions:Q9H5B0,created: Oct 16, 2001.
            sequence updated: Oct 16, 2001.
            annotation updated: Jun 15, 2002.
            xrefs: gi: 10185396, gi: 10944516
            xrefs (non-sequence databases): InterPro IPR000276, Pfam PF00001,
            PRINTS PR00237, PROSITE PS00237, PROSITE PS50262
KEYWORDS    G-protein coupled receptor; Transmembrane; Glycoprotein; Multigene
            family; Olfaction.
SOURCE      human.
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 313)
  AUTHORS   Williams,S.
  TITLE     Direct Submission
  JOURNAL   Submitted (~OCT-2000)
  REMARK    SEQUENCE FROM N.A.
COMMENT     ---------------------------------------------------------------------
            This SWISS-PROT entry is copyright. It is produced through a
            collaboration between the Swiss Institute of Bioinformatics and
            the EMBL outstation - the European Bioinformatics Institute.
            The original entry is available from http://www.expasy.ch/sprot
            and http://www.ebi.ac.uk/sprot
            ---------------------------------------------------------------------.
            [FUNCTION] PUTATIVE ODORANT RECEPTOR.
            [SUBCELLULAR LOCATION] Integral membrane protein.
            [SIMILARITY] BELONGS TO FAMILY 1 OF G-PROTEIN COUPLED RECEPTORS.
FEATURES             Location/Qualifiers
     source          1..313
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
     gene            1..313
                     /gene="OR2B6"
     Protein         1..313
                     /gene="OR2B6"
                     /product="Olfactory receptor 2B6"
     Region          1..25
                     /gene="OR2B6"
                     /region_name="Domain"
```

☐ 1: P58173. Olfactory recepto... BLink, Domains, Related Sequences, Domain Relatives, Taxonomy, LinkOut

[gi:14423785] /gene="OR2B6"

```
0..100
in"
           bond(97,189)
)
    /gene="OR2B6"
       /bond_type="disulfide"
Y SIMILARITY."
         101..120
              /region_name="Transmembrane region"
egion"
L)."
        /gene="OR2B6"
        /note="CYTOPLASMIC (POTENTIAL)."
   140..158
e="Transmembrane region"
              /note="4 (POTENTIAL)."
e="4 (POTENTIAL)."
gion          159..195
  /region_name="Domain"
NTIAL)."
..219
   /gene="OR2B6"
        /region_name="Transmembrane region"
e region"
/note="5 (POTENTIAL)."
e="OR2B6"
 /note="CYTOPLASMIC (POTENTIAL)."
          /gene="OR2B6"
 region"
0..272
                 /region_name="Domain"
R (POTENTIAL)."
                  /gene="OR2B6"
name="Transmembrane region"
Region          293..313
       /gene="OR2B6"
              /region_name="Domain"
          /note="CYTOPLASMIC (POTENTIAL)."

siiq efillgfsdr pwlefpllvv flisytvtif gnltiilvsr ldtklhtpmy
if gnltiilvsr ldtklhtpmy
  61 ffltnlslld lcyttctvpq mlvnlcsirk visyrgcvaq lfiflalgat eylllavmsf
rk visyrgcvaq lfiflalgat eylllavmsf
l hysvimhqrl clqlaaaswv tgfsnsvwls tltlqlplcd pyvidhflce
svwls tltlqlplcd pyvidhflce
81 vpallklscv ettaneaelf lvselfhlip ltlilisyaf ivravlriqs aegrqkafgt
```

```
                     /note="EXTRACELLULAR (POTENTIAL)."
     Site            5
                     /gene="OR2B6"
                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
     Region          26..49
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="1 (POTENTIAL)."
     Region          50..57
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="CYTOPLASMIC (POTENTIAL)."
     Region          58..79
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="2 (POTENTIAL)."
     Region          80..100
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="EXTRACELLULAR (POTENTIAL)."
     Bond            bond(97,189)
                     /gene="OR2B6"
                     /bond_type="disulfide"
                     /note="BY SIMILARITY."
     Region          101..120
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="3 (POTENTIAL)."
     Region          121..139
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="CYTOPLASMIC (POTENTIAL)."
     Region          140..158
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="4 (POTENTIAL)."
     Region          159..195
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="EXTRACELLULAR (POTENTIAL)."
     Region          196..219
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="5 (POTENTIAL)."
     Region          220..236
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="CYTOPLASMIC (POTENTIAL)."
     Region          237..259
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
                     /note="6 (POTENTIAL)."
     Region          260..272
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="EXTRACELLULAR (POTENTIAL)."
     Region          273..292
                     /gene="OR2B6"
                     /region_name="Transmembrane region"
```

```
                     /note="7 (POTENTIAL)."
     Region          293..313
                     /gene="OR2B6"
                     /region_name="Domain"
                     /note="CYTOPLASMIC (POTENTIAL)."
ORIGIN
        1 mnwvndsiiq efillgfsdr pwlefpllvv flisytvtif gnltiilvsr ldtklhtpmy
       61 ffltnlslld lcyttctvpq mlvnlcsirk visyrgcvaq lfiflalgat eylllavmsf
      121 drfvaicrpl hysvimhqrl clqlaaaswv tgfsnsvwls tltlqlplcd pyvidhflce
      181 vpallklscv ettaneaelf lvselfhlip ltlilisyaf ivravlriqs aegrqkafgt
      241 cgshlivvsl fystavsvyl qppspsskdq gkmvslfygi iapmlnpliy tlrnkevkeg
      301 fkrlvarvfl ikk
//
```

Revised: October 24, 2001.

Jun 12 2002 10:51:26